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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,103	09/15/2006	Yukihiko Mashima	Q96480	9096

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EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
04/20/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/593,103	MASHIMA, YUKIHIKO	
	Examiner	Art Unit	
	AMANDA SHAW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/29/2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,11-37 and 40-42* is/are pending in the application.

4a) Of the above claim(s) *1,11,12 and 14-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 4, 13, and 40-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 29, 2010 has been entered.

2. Claims 1-2, 4, 11-37, and 40-42 are currently pending.

Claims 2 and 13 have been amended.

Claims 1, 11-12, 14-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on June 24, 2009.

Previously the claims were examined to the extent that they read on the elected polymorphisms: the 1105 T>C polymorphism of the myocilin gene (Phe369Leu), the 412G>A polymorphism of the optineurin gene, and the CGG to CAG substitution at codon 114 of the noelin 2 gene (Arg144Gln). However as amended the claims no longer encompass the 412G>A polymorphism of the optineurin gene. As such the claims will be examined to the extent that they read on the remaining elected polymorphisms: the 1105 T>C polymorphism of the myocilin gene (Phe369Leu) and the CGG to CAG

substitution at codon 114 of the noelin 2 gene (Arg144Gln). The additionally recited polymorphisms have been withdrawn from consideration as being directed to a non elected invention. Prior to allowance of the claim, any non-elected subject matter that is not rejoined with any allowed elected subject matter will be required to be removed from the claims.

Withdrawn Rejections

3. The rejection made under 35 USC 112 2nd paragraph in section 4 of the Office Action of April 29, 2010 is withdrawn in view of the amendment made to the claims.

The rejection made under 35 USC 103 in section 5 of the Office Action of April 29, 2010 is withdrawn in view of the amendment made to the claims.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 4, 13, and 40-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 4, 13, and 40-42 are rejected over the recitation of the phrase “said patient” in claim 2 part (iii). There is insufficient antecedent basis for this limitation in the claim. This rejection could be overcome by amending the claim to recite “said patient”.

Claim Rejections - 35 USC § 112 1st paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4, 13, and 40-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Invention and Scope of the Claims

The claims are drawn to a method for diagnosing or predicting susceptibility to open angle glaucoma in a human subject. The claims require: obtaining a biological sample from the subject, analyzing said sample to determine the nucleotide at position 462 of the Noelin 2 gene and the nucleotide at position 1105 of the Myocilin gene of said subject, and making a diagnosis that said subject has or is susceptible to open angle glaucoma when said subject has at least one polymorphism selected from the group consisting of an adenine at position 462 of the Noelin 2 gene and a cytosine at position 1105 of the Myocilin gene.

The nature of the invention requires a reliable association between the presence of these polymorphisms and open angle glaucoma.

Teachings in the Specification and Examples:

Example 5 in the specification discusses a novel myocilin (MYOC) gene mutation, PHe369Leu, found in Japanese patients with primary open angle glaucoma (POAG). Blood samples were taken from 171 POAG patients and 100 normal subjects. Genomic DNA was isolated from the blood samples and seven exons of the MYOC gene were amplified by PCR. Then the PCR products were injected into a chromatograph for analysis using the WAVE System for DHPLC analysis. When abnormal chromatographic patterns were detected the sample that showed the abnormal chromatographic pattern was sequenced using the ABI310 automated sequencer. Four glaucoma causing mutations were identified in 5 of 171 patients with POAG (See Table 12). The 1105T>C polymorphism (Phe369Leu) was detected in 1/171 POAG patients. This mutation was not present in any of the 100 controls.

Example 12 in the specification discusses variants in the noelin 2 gene in Japanese patients with open angle glaucoma. Blood samples were taken from 276 POAG patients, 340 NTG patients and 300 normal subjects. Here it is noted that NTG comprises one third of POAG and thus is considered a subset of POAG. Genomic DNA was isolated from the blood samples and 6 exons of the noelin 2 gene were amplified by PCR. Then the PCR products were injected into a chromatograph for analysis using the WAVE System for DHPLC analysis. When abnormal chromatographic patterns were detected the sample that showed the abnormal chromatographic pattern was sequenced using the ABI310 automated sequencer. Ten sequence changes were identified in the glaucoma patients and control subjects (See Table 42). The CGG to

CAG substitution at codon 144 (Arg144Gln) was detected in 1/276 POAG patients, 1/340 NTG patients, and 0/300 controls.

The Predictability or Unpredictability of the Art:

While the state of the art with regard to the detection of polymorphisms is high, the unpredictability with regard to the association of a polymorphism with a particular phenotype (such as open angle glaucoma) is even higher.

The instant specification teaches two mutations that are possibly associated with open angle glaucoma. The c.1105 T>C (Phe369Leu) mutation in the MYOC gene was detected in 1 out of 171 patients with POAG and was not present in 100 normal Japanese subjects. The C426G>A (Arg144Gln) mutation in the Noelin gene was detected in 1 out of 276 patients with POAG, 1 out of 340 patients with NTG, and was not present in 300 controls. Here it is noted that the specification does not provide p values for the associations. The prior art of Thisted (The University of Chicago1998) provides guidance as to what is required to indicate that an association is statistically significant (Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion). Therefore without p- values (or an equivalent measure), one can not determine if the results of a particular study are statistically significant.

The claimed method of diagnosing or predicting susceptibility to open angle glaucoma by detecting the presence of a mutation in the Myocilin gene or the Noelin 2

gene is unpredictable because it was well known in the art that most gene association studies are typically wrong. Lucentini (The Scientist 2004 Vol 18 pages 1-3) teaches that it is strikingly common for follow-up studies to find gene- disease associations wrong (page 2). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (page 2). Lucentini teaches that bigger sample sizes and more family-based studies, along with revised statistical methods should be included in the gene association studies (page 3). Additionally Tabor (Nature Reviews Genetics 2002 Vol 3 pages 1-7) teaches that significant findings of association in many candidate gene studies have not been replicated when followed up in subsequent associations studies (Page 1, Column 3). Tabor further indicates that the outcomes of association studies are greatly influenced by the characteristics of the study including the size of the population studied and the number of variables analyzed. Findings of association can be influenced by problems such as selection bias, recall bias, misclassification and confounding. Significant associations might be casual or might simply be the result of coincidence or bias (Page 2, Column 1). Further Wacholder et al (J. Natl. Cancer Institute 2004Vol 96 pages 434-442) notes that "too many reports of associations between genetic variants and common cancer sites and other complex diseases are false positives (see abstract). Wacholder further teaches that there is a high chance that an initial statistically significant finding will turn out to be a false positive finding even for large, well designed, and well conducted studies (Page 434 Column 1). In view of these references the finding that the c.1105 T>C

(Phe369Leu) mutation in the MYOC gene was detected in 1 out of 171 patients with POAG and was not present in 100 normal Japanese subjects does not necessarily mean this mutation is the cause of the open angle glaucoma. The finding that the C426G>A (Arg144Gln) mutation in the Noelin gene was detected in 1 out of 276 patients with POAG, 1 out of 340 patients with NTG, and was not present in 300 controls does not necessarily mean this mutation is the cause of the open angle glaucoma.

Quantity of Experimentation Necessary:

The specification teaches two mutations that are possibly associated with open angle glaucoma. The c.1105 T>C (Phe369Leu) mutation in the MYOC gene was detected in 1 out of 171 patients with POAG and was not present in 100 normal Japanese subjects. The C426G>A (Arg144Gln) mutation in the Noelin gene was detected in 1 out of 276 patients with POAG, 1 out of 340 patients with NTG, and was not present in 300 controls. Because Lucentini (The Scientist 2004 Vol 18 pages 1-3) teaches that it is strikingly common for follow-up studies to find gene- disease associations wrong, additional experimentation would be required to determine if these polymorphisms can be used to diagnose or predict susceptibility to open angle glaucoma. Specifically Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (page 2). Therefore additional experimentation is needed to confirm the findings in the instant specification. Such experimentation would involve sequencing the MYOC and noelin-2 genes of a

bigger sample size of affected individuals having open angle glaucoma and controls. Then statistical analysis would have to be performed to determine if the mutations are associated with open angle glaucoma and to do determine if they can be used diagnostically. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment.

Conclusions:

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the guidance provided by the applicant and the specific examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention as broadly claimed.

Conclusion

6. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Amanda Shaw/
Examiner 1634